REMARKS

The Official Action dated November 16, 2006 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 9, 23 and 26 have been amended to recite an initial step of selecting an individual known to be allergic. Support for this limitation may be found throughout the present specification, for example in the Examples. At page 4, under "Materials and Methods", the subjects of the Examples are described as "weed pollen allergic patients". In the Examples, the methods of the present invention were conducted in order to determine the actual sensitizing allergen source of the individuals known to be allergic. Claims 9 and 26 are further amended for clarity, with claim 26 also reciting that the variety of allergen pollen sources contain cross reactive proteins or epitopes, in accordance with the teachings in the specification, for example in the third paragraph on page 3. It is believed therefore that these changes do not involve any introduction of new matter, whereby entry is in order and is respectfully requested.

In the Official Action, claims 9-21 and 23 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification. The Examiner asserted that the phrase "in an individual known to be allergic" recited in claim 9 and "in an individual known to be allergic, from a variety of possible allergen sources" recited in claim 23 are not clearly supported in the specification and claims as originally filed.

This rejection is traversed and reconsideration is respectfully requested. Specifically, as noted above, the Examples set forth in the present application demonstrate methods for seriologically identifying with improved accuracy in an individual "known to be allergic" the actual sensitizing allergen source from a variety of possible allergen sources containing cross-reactive proteins or epitopes. That is, the subjects of the Examples were "weed pollen

allergic patients" and therefore known to be allergic. In fact, prior to conducting the method according to the present invention, these individuals were determined to have serum IgE Abs specific for ragweed, mugwort and/or *Parietaria* pollen extracts as set forth in Tables 1, 2 and 3. Accordingly, the specification as originally filed clearly describes to one of ordinary skill in the art a method for seriologically identifying with improved accuracy in an individual known to be allergic the actual sensitizing allergen source as recited in claims 9, 23 and 26, whereby the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn. Reconsideration is respectfully requested.

In the Official Action, claims 9-21 and 23-29 were rejected under 35 U.S.C. §102(b) as being anticipated by Duro et al, *FEBS Letters*, 399 (1996), 295-298. The Examiner asserted that Duro et al teach contacting serum with recombinant Par j 2 to detect pollen allergy and that the characterization of the recombinant antigen is a preliminary step for use of the protein therapeutically. The Examiner concluded that the prior art teaches all of the method steps of the claimed invention and therefore anticipates the claimed invention as the preamble adds no additional limitations to the claims since the same product was used in the same method steps for identifying allergens from patients. The Examiner further asserted that Duro et al teach identifying the actual sensitizing allergen (recombinant Par j 2) from a variety of possible allergen sources since Duro et al teach there are nine possible allergens in the P. judaica pollen and since the Par j 2 is the allergen selected among all allergens to perform the experiments. The Examiner also asserted that if the Par j 2 is a pure allergen component, without cross-reactivity, with use as a diagnostic tool for diagnosing specific allergy, then this information shows that 18% of the patients were not allergic to P. judaica and therefore the results inherently show that 18% of the patients were allergic to another allergen from a variety of allergen sources other than P. judaica, presumably with cross-reacting proteins or epitopes to P. judaica.

However, Applicants submit that the methods defined by claims 9-21 and 23-29 are not anticipated by and are patentably distinguishable from the teachings of Duro et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Initially, it is important to clarify the terminology employed in the present claims and specification. Allergen source refers to a particular species of plant from which individual allergen components are derived. For example, as set forth in the present specification at page 2, beginning at line 7, weed pollens constitute important allergen sources worldwide. However, allergen sources such as pollen comprise a mixture of allergic molecules which are commonly referred to as the allergen components. As explained in the introduction of Duro et al, the *Parietaria* judaica pollen is a single allergen source containing at least 9 allergen components having different molecular weights and IgE-binding specificity.

As also explained in the present application, for example at page 2, beginning at line 9, some, but not all, allergen components present in pollen of any particular allergen source, for example of a weed species such as mugwort, ragweed or wall pellitory (P. judaica), are represented by structurally similar homologs in another species and therefore show degrees of seriological cross-reactivity. It is therefore difficult or impossible to unambiguously determine an allergen source responsible for sensitization and to insure an optimal choice of selective immunotherapy using total allergen extracts. On the other hand, the present methods allow improved diagnosis of allergy by identifying the actual sensitizing allergen source, i.e., the particular weed pollen or the like, among a variety of possible allergen sources, for example from among various weed pollens, which contain cross-reactive proteins or epitopes. These methods are based on use of a pure allergen component of limited or no cross-reactivity.

More particularly, as defined by claim 9, the invention is directed to a method for serologically identifying in an individual known to be allergic the actual sensitizing allergen

source from among a variety of possible allergen sources containing cross-reactive proteins or epitopes, for example, from among mugwort, ragweed and a *Parietaria* species such as P. judaica. The method comprises selecting an individual known to be allergic and contacting serum from the individual with a pure allergen component having limited or no cross-reactivity which has been derived from one of the variety of possible allergen sources (as contrasted with an extract of the allergen source which contains a number of cross-reactive allergen components), determining, in the serum, the presence of IgE binding to the pure allergen component, and identifying the source from which said pure allergen component is derived as the actual sensitizing allergen source if the serum contains IgE binding to the pure allergen component.

According to claim 23, the invention is directed to a method for serologically identifying with improved accuracy sensitivity to *Parietaria* pollen in an individual known to be allergic, from among a variety of possible allergen pollen sources, comprising selecting an individual known to be allergic, contacting a serum sample from the individual with a pure allergen component of Par j 1 or Par j 2, determining, in the serum, the presence of IgE binding to the pure allergen component, and identifying the individual as sensitive to *Parietaria* pollen (i.e., the allergen source) if the serum contains IgE binding to the pure allergen component.

Finally, as defined by claim 26, the invention is directed to a method for serological diagnosis for an individual known to be allergic of an actual sensitizing allergen pollen source from among a variety of possible allergen pollen sources containing cross-reactive proteins or epitopes with improved accuracy. The method for serological diagnosis comprises selecting an individual known to be allergic to pollen, contacting a serum sample from the individual with a pure allergen component derived from one of the variety of allergen pollen sources and having limited or no cross-reactivity, determining, in the serum,

the presence of IgE binding to the said pure allergen component, and identifying the allergen pollen source from which the pure allergen component is derived as the actual sensitizing allergen pollen source if the serum contains IgE binding to the pure allergen component.

Thus, the present methods are for accurately identifying the actual sensitizing allergen source (for example, the actual sensitizing pollen, i.e., ragweed, mugwort of wall pellitory) from among the variety of allergen sources (for example, various weed pollens) for an individual who is already known to be allergic. Thus, one skilled in the art will appreciate that the present methods are not for generally diagnosing allergy, as the individual has already been generally diagnosed with allergy; rather, the present methods are for identifying to which particular allergen source, for example, to which pollen, the individual is allergic, which can then be used by a physician in deciding a therapeutic strategy.

The methods of the present invention are based on the surprising discovery that it is possible to identify the actual sensitizing allergen among a variety of possible allergen sources containing cross-reactive proteins or epitopes. This is done by detecting that a pure allergen component with limited or no cross-reactivity only binds to patients that are primarily sensitized to the allergen source from which the component is derived. For example, in the specific embodiment involving *Parietaria* pollen exemplified in the application, Applicants have determined that *Parietaria* pollen extract binds IgE from individuals not exposed to *Parietaria* pollen, while pure rPar j 2 does not bind to IgE from such individuals. However, rPar j 2 does bind IgE from most allergic individuals who are primarily sensitized to *Parietaria* pollen. Thus, Applicants have developed the present methods for specific identification of such an actual sensitizing allergen source among a variety of possible allergen sources containing cross-reactive proteins or epitopes by contacting serum with a pure allergen component of limited or no cross-reactivity.

More specifically, wall pellitory (*Parietaria judaica* or Par j) typically does not grow in Scandinavia or the United States, so that patients in these areas are thus not primarily sensitized to wall pellitory. Nonetheless, as shown in Tables 2 and 4 in the present specification (pages 9 and 11, respectively), these patients have IgE that specifically bind to pollen extract from wall pellitory. This is because some allergen components are cross-reactive between species, i.e., allergen pollen sources. However, none of the Scandinavian or U.S. patients have IgE that binds to the pure allergen component Par j 2, because, as Applicants have discovered, rPar j 2 lacks cross-reactivity with its homologous allergen components from ragweed (*Ambrosia artemisiifolia*, Amb a 2) and mugwort (*Artemisia vulgaris*, Art v 2). On the other hand, the Mediterranean population studied in the examples of the present application, which lives in an area where wall pellitory grows, 81% of the patients have IgE-specific for rPar j 2, as shown in Tables 3 and 4 at pages 10 and 11 of the present specification. Finally, the Australian population, living in an area where there is a low risk of exposure and primary sensitization to wall pellitory, shown only 9.5% IgE specificity for rPar j 2, as shown in Tables 1 and 4, despite 71% showing sensitivity to wall pellitory as the allergen source.

Thus, the present methods for specific identification of an actual sensitizing allergen source from among a variety of possible allergen sources containing cross-reactive proteins or epitopes provide a significant improvement in allergy diagnosis. Further, one of ordinary skill in allergy treatment will recognize the importance of making such an accurate identification from the serum sample in providing improved allergy treatment.

In the Official Action, the Examiner asserted that Duro et al teach seriologically identifying the actual sensitizing allergen from a variety of possible allergen sources. Applicants disagree as the Duro et al publication is directed to a single allergen source, namely *Parietaria judaica* pollen, and does not mention other allergen sources. While Duro

et al seek to characterize one of at least 9 allergen components of this source, namely Par j 2, Duro et al are not concerned with any other allergy source. Further, by showing that 82% of the *Parietaria judaica* pollen sensitive patients' serum had IgE reacting with rPar j 2, Duro et al merely show that Par j 2 is a major allergen (see page 297, right column, lines 18-21), and no other findings or conclusions are provided by Duro et al. Particularly, Duro et al do not teach or suggest that Par j 2, or any other pure allergen component, can be employed in order to seriologically identify with improved accuracy the actual sensitizing allergen source among a variety of possible allergen sources containing cross-reacting proteins or epitopes, as recited in the present claims.

In this regard, the Examiner states on page 4 of the Official Action "if the Par j 2 is a pure allergen component without cross-reactivity...then this information shows that 18% of the patients were not allergic to P. judaica." However, Duro et al provide no teaching or suggestion that Par j 2 is a pure allergen component with limited or no cross-reactivity. In this regard, the Examiner's attention is directed to the Declaration Under 37 C.F.R. 1.132 of the co-inventor Dr. Paolo Colombo submitted herewith. Dr. Colombo confirms that the Duro et al paper does not disclose or suggest that the Par j 2 allergen has limited or no cross-reactivity with allergen components from other allergen sources (paragraph 4) and thus Duro et al do not teach or suggest using Par j 2, or any other purified allergen component, in methods for diagnosis of the actual sensitizing source from a variety of possible allergen sources (paragraph 4). Accordingly, not only do Duro et al fail to teach any method by which an actual sensitizing allergen pollen source is identified with respect to an individual known to be allergic, Duro et al provide no teaching or suggestion that the Par j 2 discussed therein has limited or no cross-reactivity and therefore would be suitable for use in such a method.

The Examiner's assertion that Duro et al teaches nine possible allergens in P. judaica pollen and therefore identifies the actual sensitizing allergen from a variety of possible

allergen sources disregards the definition of allergen source set forth in the present application, namely, as noted above, a particular species of plant from which individual allergen components are derived. Thus, Duro et al are directed to a single allergen source. Moreover, the Examiner's assertion that because 18% of the Duro et al patients had IgE which did not react with Par j 2, these results show that 18% of the patients were allergic to another allergen from a variety of allergen sources other than P. judaica. The Examiner's assertion overlooks the fact that nothing in Duro et al teaches that Par j 2 has limited or no cross-reactivity with components of other allergen sources. Only in hindsight of the present specification can such a conclusion be made.

Thus, while Duro et al disclose the cloning and characterization of the allergen Par j 2.0101, and generally mention that in a diagnostic/therapeutic approach, a preliminary step is to purify and characterize each major allergen, this is only a general statement relating to all allergens and all diagnostic and therapeutic strategies. Applicants find no teaching or suggestion regarding any specific diagnostic method or approach. Particularly, Applicants find no teaching or suggestion by Duro et al regarding a method for accurately identifying an actual sensitizing allergen source from among a variety of possible allergen sources containing cross-reactive proteins or epitopes as required by claims 9, 23 and 26, particularly using a pure allergen component of limited or no cross-reactivity.

Moreover, claims 9, 23 and 26 recite additional steps which further illustrate the distinctions between the claimed invention and the teachings of Duro et al. Particularly, the method of claim 9 requires, in addition to selecting an individual known to be allergic and contacting serum with a pure allergen component of limited or no cross-reactivity, the steps of determining the presence of IgE binding to the pure allergen component in the serum and, if the serum contains IgE binding to the pure allergen component, identifying the allergen source from which the pure allergen component is derived as the actual sensitizing allergen

source. In the more specific embodiment of claim 23, the step of contacting a serum sample from the individual with a pure component of Par j 1 or Par j 2 is followed by similar determination and identification steps. Further, claim 26 includes not only the steps of selecting an individual known to be allergic to pollen and contacting a serum sample from the individual with a pure allergen component of limited or no cross-reactivity, but the additional steps of determining the presence of IgE binding to the pure allergen component in the serum and, if the serum contains IgE binding to the pure allergen component, identifying the allergen pollen source from which the pure allergen component is derived as the actual sensitizing allergen pollen source.

Duro et al provide no teaching, suggestion or recognition of such method steps for serologically identifying the actual sensitizing allergen source among a variety of possible allergen sources containing cross-reactive proteins or epitopes, as required by the present claims and to the contrary, directed their study to one allergen component, Par j 2, from a single allergen source, *P. judacia*. In view of the failure of Duro et al to provide any teaching or suggestion to one of ordinary skill in the art that Par j 2 allergen component is not cross-reactive with allergen components from other allergen sources, Duro et al do not teach or suggest any method for diagnosis of the actual sensitizing source from a variety of possible allergen sources (see Dr. Colombo's Declaration, paragraph 4). In contrast, according to the present methods, an individual who may, for example, have been generally diagnosed as exhibiting allergy to weed pollen, for which many cross-reactive proteins or epitopes exist, may be provided with serological identification or diagnosis with improved accuracy of the actual sensitizing allergen source. Duro et al provide no teaching or suggestion of the present methods.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference. *In*

re Robertson, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). In view of the failure of Duro et al to teach a method for serologically identifying the actual sensitizing allergen source among a variety of possible allergen sources containing cross-reactive proteins or epitopes, particularly by use of a pure allergen component having limited or no cross reactivity, Duro et al do not anticipate the methods of claims 9, 23, 26, or claims 10-21, 24, 25 or 27-29 dependent thereon.

Dependent claim 10 further demonstrates the deficiencies in the teachings of Duro et al. Claim 10 recites the method according to claim 9, further comprising selecting an allergy treatment involving extract, proteins or peptides derived from said actual sensitizing allergen source. One skilled in the art will recognize the significance of the present methods in the ability to select a safe and effective treatment of this type. Not only do Duro et al fail to teach the methods of claim 9, 23 and 26, Applicants find no teaching by Duro et al regarding a method which includes selecting treatment involving extract, proteins or peptides derived from said actual sensitizing allergen source. Duro et al's brief reference to plan a diagnostic and therapeutic approach to allergic reaction, does not teach or suggest methods as presently claimed.

Accordingly, the methods defined by claims 9-21 and 23-29 are not anticipated by and are patentable over Duro et al, whereby the rejection under 35 U.S.C. §102 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§102 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the Examiner finds that a telephone discussion may assist in progressing the present prosecution, she is respectfully requested to contact the undersigned.

Respectfully submitted,

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